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The Preparation and Mydriatic Action of the Diethylaminoethyl Ester of Mandelic Acid

THE PREPARATION AND MYDRIATIC ACTION OF THE DIETHYLAMINOETHYL ESTER OF MANDELIC ACID

BY

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY

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Dortha B. Bailey

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INTRODUCTION.

Modern workers in chemical research on drugs recognize the fact that in general there is some relation between the chemical constitution of a drug and the effect which it produces upon the living organism. The great advances which have been made in our chemical knowledge of drugs can be traced to this viewpoint. In general, such research has been developed along three main lines.

1. The natural product is carefully analyzed and its structure determined.

2. This natural product is compared with other compounds having a like physiological action to determine any similarities in structure. The nature of the active principle can often be concluded from such a study.

3. New compounds containing these active groups are synthesized in the laboratory and their physiological action compared with that of the natural products.

An immense amount of work has been done along these lines on anaesthetics. For example, myriads of compounds have been made which center around cocaine in structure and in action as a drug. Mydriatics, those compounds which dilate the pupil of the eye, have not been studied as extensively as anaesthetics.

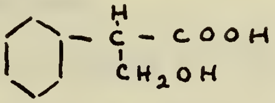
The purpose of this research was to synthesize the diethylaminoethyl ester of mandelic acid and note its mydriatic effect.

HISTORICAL AND THEORETICAL.

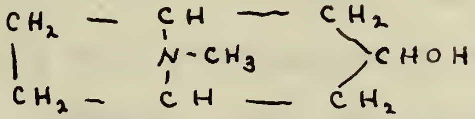
A. Atropine.

Atropine is the main compound around which the study of mydriatics has centered. Atropine is an alkaloid which occurs in the roots of the deadly night shade. Its mydriatic action is due to the ability to paralyze the motor nerve endings of the contractor muscle of the pupil of the eye. Atropine was discovered in 1831 almost simultaneously by Mein and by Geiger and Hesse. In 1863 Kraut hydrolyzed it by means of alkali or acid into two parts, a basic substance which he called tropine, and an acid, tropic acid. Lossen, the following year, was able to repeat Kraut's experiments.(1)

Tropic acid was synthesized by Ladenburg and Rugheimer in 1880 and this structure assigned to it.(2)

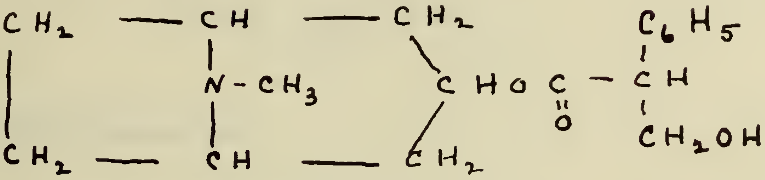


The structure of the base was not so easily determined. Our knowledge of tropine is due chiefly to the researches of Ladenburg, Merling and later Willstätter.(3) The synthesis of tropine by Willstätter confirmed the structure which had previously been assigned to it.(4)



As soon as the structures of tropine and tropic acid had been established, it was easy to picture the formula for atropine,

since it was clearly an ester of these two. Ladenburg in 1879 had synthesized atropine by esterifying tropine with tropic acid.(5) Atropine was then given this structure:

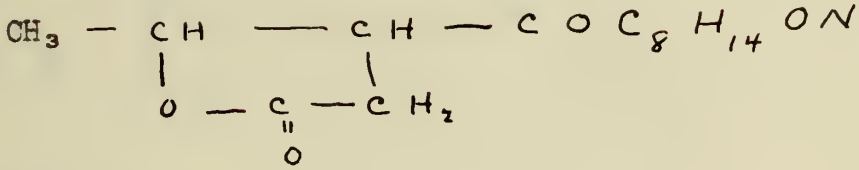


Atropine as found in nature is optically inactive. Hyoscyamine, another naturally occurring product, has been shown by Gadamer to be the ester of tropine with l. tropic acid.(6) This ester with the laevo acid is one hundred times as active as a mydriatic as the corresponding ester with the dextro acid. This is an example of the effect of optical isomerism upon mydriatic action.

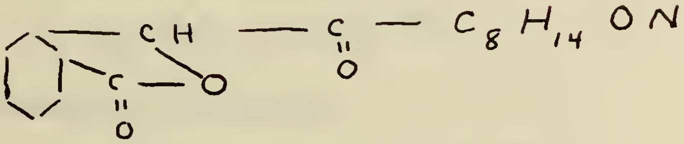
B. The Tropeines.

The next advance in the study of these compounds was the preparation of other esters of tropine. While tropine itself has no mydriatic action, it was found that many of these esters showed the same effect as atropine. Ladenburg in 1880 combined tropine with various organic acids and called these esters tropeines. He used such acids as salicylic, mandelic, phthalic, benzoic and oxybenzoic.(7) Following the work by Ladenburg, a great many tropeines were synthesized by other investigators. Liebermann, Merck, Buchheim, Petit and Polonowsky, Jowett and Hahn have all been active workers in this field.(8) Merck used aliphatic acids such as lactic, acetic, succinic, malic, tartaric.

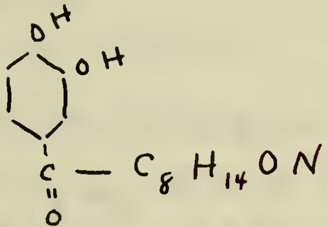
Jowett and Hahn prepared more complex tropeines as methylparaconyltropeine,



phthalidecarboxyltropeine,



protocatechyltropeine,

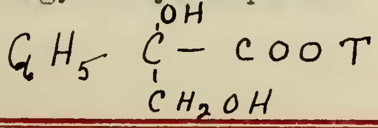


In 1917 Frank Lee Pyman published the results of a rather extensive investigation carried on by him and Dr. H. A. D. Jowett, Dr. H. H. Dale and Dr. C. R. Marshall.(9) The purpose of their research was to study the relation between the chemical constitution and physiological action of the tropeines. About forty-five tropeines were prepared and examined, for mydriatic action. None of the compounds prepared were as active as atropine itself. Some of the results of their work might be given in tabulated form.

I. Most active Atropine

II. Somewhat less active than atropine

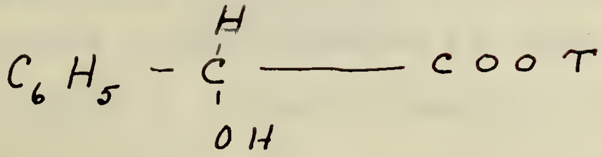
Atrogylceryltropeine



$$C_6H_5\ \underset{CH_2OH}{\overset{OH}{C}}-COOT$$

III. Still less active

Homatropine



$$C_6H_5-\overset{H}{\underset{OH}{C}}-COOT$$

IV. Faintly active

Phenylchloroacetyltropeine

$CH\ C_6H_5Cl\ COOT$

Phenylaminoacetyltropeine

$CH\ C_6H_5-(NH_2)\ COOT$

Benzoyltropeine

$C_6H_5\ COOT$

(o) Hydroxylbenzoyltropeine

$OH\ C_6H_4\ COOT$

V. Inactive

Acetyltropeine CH_3COOT

Glycollyltropeine $CH_2OHCOOT$

Lactyltropeine $CH_3CHOHCOOT$

Succinyltropeine $(CH_2COOT)_2$

None of the tropeines from aliphatic fatty acids caused mydriasis in dilute solution. Gottlieb however, reports that lactyltropeine is active if brought in the solid state on the conjunctival sac of a cat.(10)

Homatropine, the mandelic acid ester of tropine $C_6H_5CHOHCOOT$ is by far the most important of the tropeines. This had been

prepared by Ladenburg in 1883 and showed marked mydriatic action(11)

A generalization concerning chemical structure and mydriatic action of the tropeines is found in the literature as "Ladenburg's Rule." Although Ladenburg himself never formulated such a generalization. This states that a tropeine to be mydriatic, must contain:

1. A benzene nucleus in the acid radicle.
2. An alcoholic hydroxyl group in the side chain containing the carboxyl group.

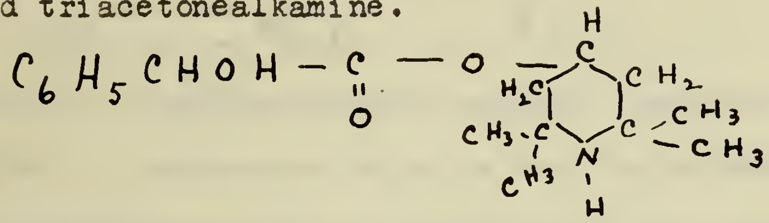
Jowett and Pyman in their investigations conclude that the first prerequisite is approximately correct since none of the aliphatic acids gave mydriatic compounds. The aromatic ring however, may be pyridine rather than benzene as they found that β 2 pyridyl α hydroxypropionyltropeine was active $(C_6H_4NCH_2CHOH)$ COOT

The second prerequisite is not correct. Mydriatic substances are obtained when the hydroxyl group of atropine is exchanged for acetoxyl, chlorine or bromine. The hydroxyl group of homatropine may be exchanged for hydrogen, chlorine, or an amino group. Benzoyl and (o) (m) hydroxybenzoyltropeines are also mydriatic. All those tropeines, however, which were found to be the most active in causing mydriasis contained the alcoholic hydroxyl group.

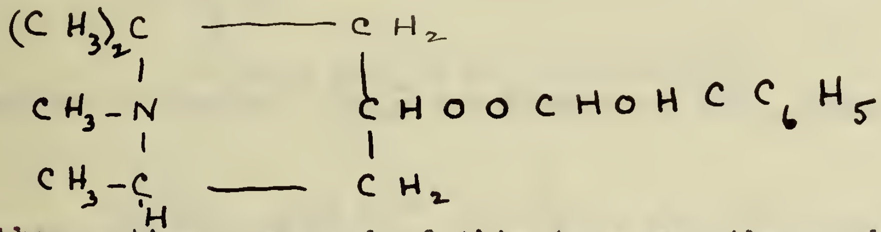
C. The Alkamine Esters.

The next logical step in the study of mydriatics was the substitution of other amino alcohols for tropine. A large number of such compounds have been prepared and are called aminoalkyl esters or alkamine esters.

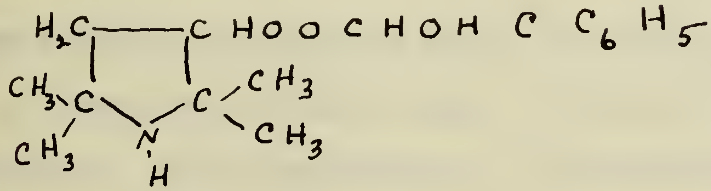
Since mandelic acid and tropine gave the best mydriatic, mandelic acid was used in many of these new compounds. Emil Fischer made an active alkamine ester by esterifying mandelic acid and triacetonealkamine.



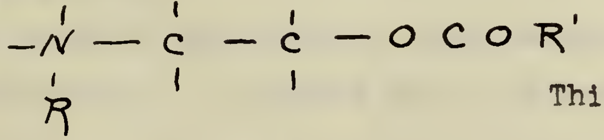
The mandelic ester of N methylvinyldiacetonalkamine furnished an example of the effect of stereoisomerism. One of the isomers was found to be active, while the other was inactive.



Another active compound of this type was the mandelic ester of β hydroxytetramethylpyrrolidine.(12)



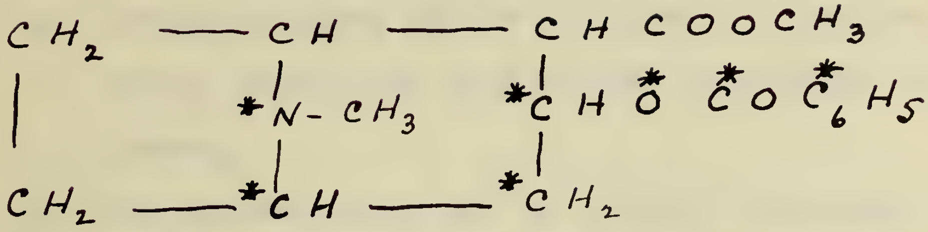
In more recent years in the study of anaesthetics, many straight chain alkamine esters have been synthesized. These have the general grouping



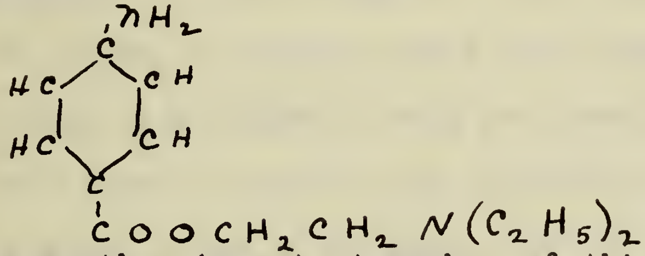
$$-\underset{R}{\overset{|}{N}}-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-OCOR'$$

This grouping is very similar to the grouping found in the active part of the cocaine

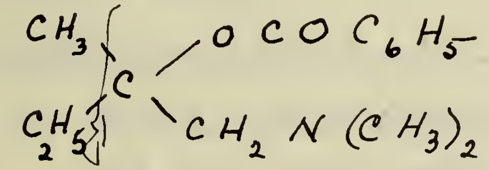
molecule



The esters of diethylaminoethyl alcohol have been studied in most detail. Novocaine which is the diethylamino ethyl ester of (p) aminobenzoic acid is probably the best known of this class of compounds.(13)



Stovaine is another important member of this group.



The German Patent literature gives the preparation of a large number of compounds of this type. A few of the acids used, might be mentioned: (p) nitrobenzoic, (p) aminobenzoic, salicylic, benzoic, N dimethylanthranilic, (p) nitrocinnamic.(14) Most of these compounds show some action as local anaesthetics. Evidently no definite generalization can be made. Pyman attempts to draw up certain general conclusions with regard to these compounds as local anaesthetics, but makes no statement with regard to mydriatic properties. He says that in the local anaesthetics:

1. the acyl group is usually aromatic,
2. the amino group may be secondary or tertiary and may be associated with simple or bridged ring complexes,
3. the alcohol group may be primary, secondary, or tertiary and may separate the acyl and amino groups by a chain of either two or three carbon atoms.

From the above considerations it would seem that the diethylaminoethyl ester of mandelic acid might show mydriatic action. The ester of mandelic acid with tropine was active. The alkamine esters with mandelic acid as prepared by Fischer were active. The present research was undertaken then, to prepare the diethylaminoethyl ester of mandelic acid and to find out whether it had mydriatic action.

D. Methods Available for the Preparation of Alkamine Esters.

I. Direct Esterification.

The most direct method of preparing the diethylaminoethyl ester of mandelic acid, is, of course, the esterification of mandelic acid with diethylaminoethyl alcohol.

$$C_6H_5CHOHCOO\boxed{HHO}CH_2CH_2\ N(C_2H_5)_2 \rightarrow C_6H_5CHOHCOOCH_2CH_2N(C_2H_5)_2$$

This general method had been used by Ladenburg in the preparation of the tropeines. He merely heated tropine with the acid on a water bath for several days. Dilute hydrochloric acid was used as a catalyst and the amount which was lost by evaporation was replaced from time to time. Full directions for this method as applied to lactic acid and tropine are given in the literature by Ladenburg.(15)

A shorter method which gives better yields is reported by Dr. Ernst Tauber. This consists in refluxing the mixture of acid and alcohol on an oil bath 110°-120° C. for 3-4 hours. A rapid stream of dry hydrochloric gas is passed in during the heating.(16) This direct esterification has also been used successfully in making some of the alkamine esters. Salicylic acid and diethylaminoethyl alcohol can be esterified in this manner as can also N dimethyl anthranilic acid and diethylaminoethyl alcohol.(17)

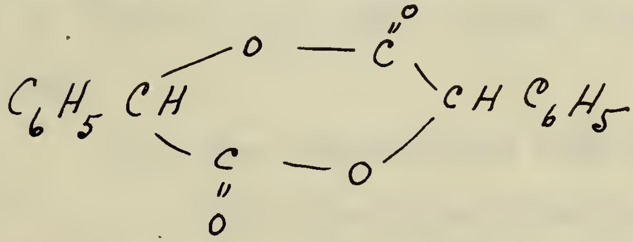
The method which was first tried in this research was that of Dr. Ernst Tauber for the preparation of the ester of mandelic acid and tropine. The mandelic acid and diethylaminoethyl alcohol were heated on an oil bath 110°-120°C. and hydrochloric acid gas passed in. The resulting product was made alkaline and extracted with chloroform as described in the experimental part. A very small amount of a dark brown oil was obtained. It was practically insoluble in hydrochloric acid which made it seem unlikely that it was the ester. Several runs were made, using this method and one run was made using the longer method of Ladenburg. The results were exactly the same in every case. The product obtained might have been the ester. The yield was so small, however, that this method was abandoned without attempting to determine this fact.

II. The Reaction of Acid Chlorides with Amino Alcohols.

Amino alcohols as a class do not react readily with acids to form esters. The reaction of the amino alcohol

and the chloride of the acid as a rule proceeds much more smoothly. Some of the tropeines and the alkamine esters have been prepared by the use of the acid chlorides. The acid chloride of (p) aminobenzoic acid reacts easily with oxyethylpiperidin: (p) nitrocinnamic acid chloride and diethylaminoethyl alcohol react to give the corresponding ester.(18)

An attempt was made to prepare the acid chloride of mandelic acid. The presence of a hydroxyl group in the side chain made it necessary to avoid the use of PCl_5, which is ordinarily used in making acid chlorides. R. Wolfenstein has devised a method of preparing the acid chlorides of oxyacids which has been used successfully in the case of salicylic acid. This consists in treating the acid with thionyl chloride($SOCl_2$) in benzene solution(19). This method was tried with mandelic acid, but with negative results. McKenzie and Clough in the course of experiments on Walden's Inversion, report the formation of the chlor derivative ($C_6H_5CHClCOCl$) by treating mandelic acid with $SOCl_2$(20). $COCl_2$ in pyridin had been used by Hollandt in the preparation of certain acid chlorides.(21) Einhorn and Mettler in some experiments with various acids and $COCl_2$ in pyridin found that two molecules of mandelic acid combined to give a complex compound.(22)



The $SOCl_2$ might have caused a similar reaction to take place. At

any rate, the method did not seem promising enough to spend a great deal of time on it.

III. The Reaction of the Chlorethyl Ester with Diethylamine.

A third method which has been used frequently in the synthesis of the alkamine esters is the formation of the chlorethyl ester of the acid and subsequent condensation with diethylamine. The chlorethyl ester is made by treating the acid with ethylene chlorhydrin ($OHCH_2CH_2Cl$). The alkamine esters of (p) aminobenzoic acid, salicylic acid and benzoic acid for example, have been made by this method.(23)

(a) The Preparation of the Chlorethyl Ester.

The method used for the preparation of the chlorethyl ester of mandelic acid was similar

$$C_6H_5CHOHCOOCH_2CH_2Cl$$

to that described by Emil Fischer and Arthur Speier for the synthesis of the ethyl ester of mandelic acid.(24) This consisted in refluxing the two constituents for four hours using concentrated H_2SO_4 as a catalytic agent. The product was made alkaline, extracted with ether and the ester distilled in vacuo. The vacuum was poor on the first run and the ester evidently decomposed. By distilling at 8-10 mm. pressure, a good product was obtained which boiled at 150° C.

(b) The Condensation with Diethylamine.

The directions given in the literature for the condensation of chlorethyl esters with diethylamine direct

heating for ten hours at 100°-120°C. in a sealed tube.(25) The mandelic acid chlorethyl ester ($C_6H_5CHOHCOOCH_2CH_2Cl$) was sealed up with an excess of diethylamine and heated as directed. Crystals of diethylamine hydrochloride separated out in the tube showing that a reaction had taken place. The oil was separated by ether extraction. An unsuccessful attempt was made to obtain a solid hydrochloride or hydrobromide of this base. The amounts which were used in the bomb tube were so small that a vacuum distillation to purify the product was not possible. It was later found that the chlorethyl ester would react with diethylamine by simply refluxing over night on the steam cone. This proved to be the most convenient and satisfactory method as it made the use of larger quantities possible and eliminated the use of sealed tubes. The final ester $C_6H_5CHOHCH_2CH_2N(C_2H_5)_2$ was obtained as a brown oil which was purified by vacuum distillation.

IV. The Reaction of the Bromo and Iodoethyl Ester with Diethylamine.

It was believed that the bromo or iodo compounds would react more easily with diethylamine than the corresponding chlor compound. Bromohydrin was therefore prepared by the action of ethylene gas on bromine water under conditions devised by John Read and Margaret Mary Williams.(26) The bromoethyl ester of mandelic acid was synthesized in the same way as the corresponding chlor compound. It was found that this would react in the cold with diethylamine. Another experiment was carried on to replace the chlorine in the chlorethyl ester of mandelic acid by

iodine. The chlorethyl ester was refluxed in dry acetone with an equivalent amount of sodium iodide (NaI). Some sodium chloride separated out showing that some reaction had taken place. The sodium chloride which separated out however, was only a small percent of the amount which should have been formed if the action had gone to completion. This mixture of the chlorethyl ester and the iodoethyl ester when treated with diethylamine reacted in the cold. This method did not prove as satisfactory as the use of the chlor compound.

EXPERIMENTAL

I. Preparation of Mandelic Acid ($C_6H_5CHOHCOOH$)

250 grams of benzaldehyde C_6H_5CHO were added in small portions with stirring to a saturated solution of sodium bisulfite ($NaHSO_3$), (945 grams). The solution was cooled and allowed to stand ten minutes. The thick pasty mass of the bisulfite addition product was filtered with suction and washed with a very little water. It was then placed in a flask and enough water added to make it just fluid. To this mixture a solution of 204 grams sodium cyanide(NaCN) in 300 cc. of water was added in small portions with shaking. A colorless oil separated which turned red in 8-10 minutes. This nitrile was separated quickly in a separatory funnel and poured into an evaporating dish. Not all of the benzaldehyde addition product reacts at once so about 30 grams of sodium cyanide (NaCN) in 300 cc. of water was added and the flask again shaken vigorously. More of the nitrile separated by this treatment. Not more than 15 minutes should elapse between the addition of the NaCN solution and the last extraction. 600 cc. of concentrated hydrochloric acid were added to the nitrile with stirring and the dish placed on the steam cone. The first heavy white precipitate consisted almost entirely of NH_4Cl and was filtered off. The filtrate was evaporated almost to dryness and filtered. The powder, thoroughly dried, was extracted with hot benzene. The mandelic acid used in the earlier experiments was nearly pure, M.P. 116° C. The true M. P. is 118° C. It was later found that the presence of NH_4Cl did not interfere with the esterification so

that the mixture was used without attempting to remove all of the NH_4Cl.

II. (a) Attempt to Esterify Mandelic Acid with Diethylaminoethyl Alcohol.

The method used was similar to that described in the German patents for the esterification of mandelic acid and tropine (27).

15 grams of mandelic acid ($C_6H_5CHOHCOOH$), 9 grams of diethylaminoethyl alcohol $(C_2H_5)_2NCH_2CH_2OH$ and 5 cc. of water were heated on an oil bath 110°-120° C. for four hours. A strong stream of hydrochloric gas, dried by bubbling through concentrated sulphuric acid, was passed into the mixture during the heating. The reaction product was made alkaline with Na_2CO_3. A pasty mass resulted which was diluted with water and extracted with chloroform. On evaporating off the chloroform about 3 grams of a dark brown liquid remained. This should have been an ester and any of the amino alcohol which did not enter into the reaction. The diethylaminoethyl alcohol was dissolved by treatment with water, and the ester was again extracted with chloroform. During the first extraction a considerable quantity of solid material appeared in the separatory funnel. This was filtered off. A small part of it proved to be sodium carbonate. The remainder was a light brown powder. When heated on a platinum foil it behaved like inorganic matter. It was insoluble in chloroform, and ether and very difficultly soluble in water. It dissolved easily in dilute hydrochloric acid and could be reprecipitated by adding alkali.

Just what this powder was, was not determined.

The brown oil which remained after the second extraction with chloroform should have been the ester. It was only very slightly soluble in dilute hydrochloric acid which made it seem doubtful whether the ester had formed. At any rate the yield was so very small that this method was abandoned after three runs. had been made with duplicate results.

II. (b) Esterification of Mandelic Acid and Diethylaminoethyl Alcohol.

One run was made by the long method which is described in the preparation of lactyl tropein.(28) 10 grams of mandelic acid, 11 grams of diethylaminoethyl alcohol, 10 grams of concentrated hydrochloric acid were heated on a water bath for several days. The hydrochloric acid which evaporated off was replaced from time to time. The reaction mixture was then made alkaline with sodium carbonate and extracted with chloroform. No solid material separated out in this case during the extraction. On evaporating off the chloroform a small amount of a heavy dark brown oil remained which corresponded in color, odor and solubility to the product obtained by the shorter method.

III. Attempt to Prepare the Acid Chloride of Mandelic Acid. $C_6H_5CHOHCOCl$.

The method used was similar to that which can be used in the preparation of salicyl chloride. (19) 5 grams of mandelic acid, 3.6 grams of thionyl chloride ($SOCl_2$) were refluxed at the boiling point of the mixture dissolved in benzene until no

sulphur dioxide and hydrochloric acid came off. This required about one hour. The benzene and excess thionyl chloride ($SOCl_2$) were then distilled off in vacuo. A light brown viscuous oil remained. On boiling this with sodium hydroxide ($NaOH$) it was not possible to recover mandelic acid so it was concluded as doubtful whether any of the acid chloride had been formed.

Some of the oil, however, was dissolved in benzene and an equivalent amount of a benzene solution of diethylaminoethyl alcohol $(C_2H_5)_2NCH_2\ CH_2OH$ added. This mixture was allowed to stand over night and the benzene then distilled off in vacuo. A very thick brown oil was left which was insoluble in dilute hydrochloric acid.

Another run was made using 10 grams of mandelic acid and 7.2 grams of thionyl chloride in benzene solution. This was refluxed for two hours and the benzene then distilled off in vacuo. The oil which remained was then refluxed for about an hour with an equivalent quantity of diethylaminoethyl alcohol. This benzene solution was treated with dilute hydrochloric acid in an attempt to extract the basic ester. On the addition of hydrochloric acid a large amount of a heavy brown oil separated out. This was not soluble in the hydrochloric acid, but addition of a large volume of benzene took it into solution again. The hydrochloride of the ester should be water soluble. This method of preparation seemed so unsatisfactory that no more time was spent on it.

IV. The Preparation of the Chlorethyl Ester of Mandelic Acid. $C_6H_5CHOHCOOCH_2CH_2Cl$.

The method used was similar to that used by Fischer and Speier in making the ethyl ester.(24)

15 grams of mandelic acid ($C_6H_5CHOHCOOH$), 16 grams of ethylene chlorhydrin ($OHCH_2CH_2Cl$) and 4.5 grams of concentrated sulphuric acid were refluxed four hours. The reaction mixture was poured into water and made alkaline with sodium carbonate. This removed any unchanged mandelic acid and the sulphuric acid. The ester was then extracted with ether, the ether solution dried and the ester distilled in vacuo. The greater portion of the product distilled over between 80°-130° at 130 mm. pressure. Upon raising the temperature decomposition started and a black tarry mass was left. The lower boiling portions had a penetrating odor while the higher boiling portion had an odor which more nearly resembled an ester.

15 grams mandelic acid, 16 grams ethylene chlorhydrin, 1/2 cc. concentrated sulphuric acid were refluxed on a steam cone for four hours. The mixture was made alkaline with sodium carbonate and extracted with ether. In this run a smaller amount of sulphuric acid was used and the temperature was kept lower. This seemed to prevent charring somewhat. The ether extract was distilled in vacuo. The distillation began at about 50°C., 8-10 mm. pressure. About one third of the total amount came over at this temperature. This was probably unchanged ethylene chlorhydrin for the most part. After this the temperature rose gradually to 150°C. where it remained practically constant throughout the distillation. A very small amount of tarry material remained in

the flask. The portion which boiled at 150°-153° C. under 8-10 mm. pressure was a pale yellow oil which solidified upon standing over night. By cooling it could be made to solidify immediately. M.P. 42°. When recrystallized from low boiling petroleum ether it was obtained as a white powder. M. P. 44°.

One run was made using hydrochloric gas as the catalyst instead of concentrated sulphuric acid and very good results were obtained although no decided improvement over the sulphuric acid was noted.

In the preparation of the large quantity to be used later, sulphuric acid was used. From 50 grams of mandelic acid, 35 grams of the redistilled ester was obtained, a yield of about fifty percent.

A Carius determination for chloride was run upon a sample which had been purified by recrystallization from low boiling petroleum ether.

Percent. of Cl_2 found in the sample 16.3

Percent. of Cl_2 as calculated from formula 16.5

V. (a) The Condensation of the Chlorethyl Ester of Mandelic Acid $C_6H_5CHOHCOOCH_2CH_2Cl$ with Diethylamine $HN(C_2H_5)_2$

The first method tried was similar to that used by Einhorn and Uhlfelder in the condensation of (p) nitrobenzoic acid chlorethyl ester $NO_2C_6H_4COOCH_2CH_2Cl$ and diethylamine $HN(C_2H_5)_2$.(25)

2 grams of the mandelic acid chlorethyl ester and 2 grams of diethylamine were sealed in a bomb tube and heated at 100° C.

over night. The reaction mixture was an oily mass with considerable amount of crystals of diethylamine hydrochloride. The mass was treated with water to dissolve the crystals. The oil was then extracted with ether and the ether evaporated off. An attempt was made to obtain the hydrochloride of the ester as a solid. The oil was dissolved in a little alcohol and treated with hydrochloric acid in alcohol to a very faint acid reaction. The alcohol was then evaporated off. A heavy light brown oil was obtained which would not solidify. The hydrobromide was prepared and it also was a brown oil which would not solidify.

V. (b) The Condensation of the Chlorethyl Ester of Mandelic Acid with Diethylamine.

The second method used consisted in simply refluxing 15 grams of mandelic acid chlorethyl ester $C_6H_5CHOHCOOCH_2CH_2Cl$ and 15 grams of diethylamine $HN(C_2H_5)_2$ over night on the steam cone. The treatment with water and the extraction with ether was carried out as in the first method. The oil which was obtained was distilled in vacuo. About two thirds of it came over at about 60° C. under 5 mm. pressure. A constant boiling fraction was obtained at 160°-165° C. This was a light brown oil which gave a qualitative test for nitrogen and only a very faint test for chlorides. About 5 grams of this oil was obtained, a yield of about 30 percent. The nitrogen in this sample was quantitatively determined by Kjeldahl's method.

Percent. of nitrogen found 5.2 percent.

Percent of nitrogen calculated from formula 5.5 percent.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

VI. The Preparation of Ethylene Bromohydrin $OHCH_2CH_2Br$.

The method used was similar to that described by John Read and Margaret Mary Williams (26).

Well washed ethylene prepared by the action of alcohol on concentrated sulphuric acid was passed into a large separatory funnel containing 7.2 grams of bromine dissolved in 500 cc. of water. The funnel was surrounded by ice throughout the experiment and agitated frequently. As soon as the bromine water was completely decolorized another portion of 7.2 grams of bromine was added. The ethylene dibromide $BrCH_2CH_2Br$ which formed as a lower layer was drawn off from the solution at frequent intervals. This prevented the extraction of the bromine from the solution by the ethylene dibromide. The process was continued until 150 grams of bromine had been added. Any of the dibromide which had not been drawn off was now removed. The aqueous layer was neutralized with sodium carbonate and saturated with sodium chloride. The ethylene bromohydrin was extracted several times with ether and the ether solution dried over Na_2SO_4. The ether was distilled off. The bulk of the residual liquid distilled over between 145° and 149°. 35 grams of the ethylene bromohydrin were obtained.

VII. The Esterification of Mandelic Acid with Bromohydrin.

25 grams of mandelic acid, 25 grams of bromohydrin and 1 cc. of concentrated sulphuric acid were refluxed for four hours. The reaction product was treated exactly the same as the corresponding chlorine derivative. The mandelic acid bromoethyl ester ($C_6H_5CHOHCOOCH_2CH_2Br$) was obtained as a light yellow oil. B.P. 175°-

[illegible]

[illegible]

[illegible]

177° at 6 mm. pressure. It could be made to solidify on cooling but became liquid again at room temperature. The exact yield was not determined but it was between 40 percent. and 50 percent.

VIII. The Condensation of the Bromoethyl Ester of Mandelic Acid with Diethylamine.

The bromine compound reacts much more readily with diethylamine than the corresponding chlorine compound. 10 grams of the mandelic acid bromethyl ester were mixed with an excess of diethylamine and allowed to stand in the cold. The product was not observed on the following day, but two days later it was found that the reaction had taken place as the solution was impregnated with crystals of the diethylamine hydrobromide. This product was not worked up further.

IX. The Preparation of the Iodoethyl Ester of Mandelic Acid.

5 grams of mandelic acid chlorethyl ester were refluxed with 3.5 grams of NaI dissolved in dry acetone. A very small amount of sodium chloride separated out. This was filtered off and the acetone evaporated. The oil which remained was mixed with diethylamine and allowed to stand at room temperature. It was found that the condensation had taken place after a few days.

The amount of sodium chloride which separated out was not as large as the theory would demand. For this reason, a mixture of the mandelic acid chlorethyl ester and iodoethyl ester was probably obtained. This method of preparing the iodo compound was not considered very satisfactory.

X. Testing the Mydriatic Action.

Most mydriatics of this type are tested by using a one percent.solution of the hydrochloride in water. The diethylaminoethyl ester of mandelic acid was dissolved in water to make a one percent. solution and an equivalent amount of hydrochloric acid added. A few drops of this solution was put in the eye of a rabbit. No noticeable dilation resulted. A control test was made using atropine, which caused marked dilation of the pupil. One drop of the pure compound was inserted in the rabbit's eye as a further test to determine whether the compound was mydriatic. This caused marked irritation but no dilation of the pupil as far as could be seen.

SUMMARY

1. An unsuccessful attempt was made to esterify mandelic acid with diethylaminoethyl alcohol.
2. The acid chloride of mandelic acid could not be prepared by the use of $SOCl_2$ in benzene solution.
3. The diethylaminoethyl ester of mandelic acid was best prepared by making the chlorethyl ester and then condensing with diethylamine.
4. The bromoethyl ester and the iodoethyl ester reacted more easily with diethyl amine than the corresponding chlor compound. This method was not as convenient as the preceding however.
5. The diethylaminoethyl ester of mandelic acid had no mydriatic action (a) when a one percent. solution of the hydrochloride was inserted into the eye of a rabbit. (b) when a drop of the pure compound was inserted into the eye of a rabbit.

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